at page 15, lines 16-26. In addition, the specification is amended as noted by the Examiner. With regard to the amendment to the specification at page 33, the Examiner has stated on page 5 of the Action that "two alternate spliced variants have been disclosed." Applicants disagree, in that the specification describes clone #5H as the "alternate spliced variant." Thus, only one alternate spliced variant exists to the murine flt3-L clone obtained, #6C.

OBJECTIONS/REJECTIONS NOT OVER PRIOR ART:

The United States Patent and Trademark Office ("USPTO") has objected to the specification under 35 U.S.C. §112(1) as allegedly containing an inadequate description of the invention to allow the ordinary skilled artisan to make and use the invention as claimed. The USPTO has asserted various grounds as alleged support of this objection, and applicants will address each one in the order that they have been presented in the Action.

The USPTO states that the specification does not present an adequate description of what is meant by "a flt3-L polypeptide." Applicants respectfully disagree. Reference is made to page 7 of the specification, lines 11 et seq. From that description, it is clear that flt3-L refers to:

> a genus of polypeptides that bind and complex independently with flt3 receptor...

An ordinary skilled artisan would understand from the description that follows that such "genus" encompasses:

(a) (i) proteins having the amino acid sequence 1 to 231 of SEQ ID NO:2 or the amino acid sequence 1 to 235 of SEQ ID NO:6, (ii) those proteins having a high degree of similarity or a high degree of identity with the proteins of (i) and which proteins are biologically active and bind the flt3 receptor;

(b) biologically active gene products of the DNA of SEQ ID NO:1 or SEQ ID NO:5; and

(c) the membrane-bound proteins (which include an intracellular region, a membrane region, and an extracellular region), and soluble or truncated proteins which comprise primarily the extracellular portion of the protein, retain biological activity and are capable of being secreted. Specific examples of such soluble proteins are those comprising the sequence of amino acids 28-163 of SEQ ID NO:2 and amino acids 28-160 of SEQ ID NO:6.

The description is clear that such polypeptides are "biologically active." The USPTO is incorrect in alleging that the term "biologically active" is not clearly defined in the specification. Indeed, the definition states:

> the flt3-L is capable of binding to flt3. Alternatively, "biologically active" means that the flt3-L is capable of transducing a signal to the cell through the membrane-bound flt3.

The USPTO alleges that there is an apparent contradiction in such definition, however, the ordinary skilled artisan would recognize, that it is the binding to flt3, which is the *minimum*

requirement for biological activity. The USPTO is correct in that transducing a signal to a cell through a membrane-bound molecule may not be possible without first *binding to* such membrane-bound molecule. However, the specification is clear that "biologically active" means that the flt3-L must bind flt3, but either may or may not transduce a signal to the cell. A failure to transduce signal to the cell may not be exclusively caused by the ligand and may result from defects in the receptor. Thus, failure to transduce a signal to the cell is not the test, rather it is the binding to flt3 receptor that indicates the ligand's biological activity.

Thus, those polypeptides that are full length proteins as shown in SEQ ID NOS:2 and 6, the proteins having a high degree of similarity to or a high degree of identity with the proteins of SEQ ID NOS: 2 or 6, the soluble or truncated proteins comprising the sequence of amino acids 28-163 of SEQ ID NO:2 and amino acids 28-160 of SEQ ID NO:6, and the gene products of the DNA of SEQ ID NO:1 or SEQ ID NO:5 - all of which bind flt3 receptor, are encompassed by the term "flt3-L polypeptide."

The USPTO also alleges that Example 7 "is not clear." Applicants disagree that the Example is not clear. Indeed, in the last paragraph of the Example, it is stated that the flt3-L is contained in the "culture supernatant from CV-1/EBNA cells transfected with flt3-L cDNA", and for the data in Table I, isolated flt3-L from yeast was used. Applicants do not understand why the USPTO believes this to be an issue for objecting to the specification. Certainly, one of ordinary skill in the art would still be able to make and use the claimed invention notwithstanding Example 7. Example 7, or any example for that matter, is not required for enablement. Flt3-L used in any of the forms listed would work in those experiments. This is clearly stated in the Example. Withdrawal is requested.

Beginning at page 7 of the Action, the USPTO alleges that "[e]nablement of the current specification as filed is not commensurate in scope with claims to nucleic acids encoding any and all possible ligands of the flt3 receptor." The USPTO also argues that:

> receptors may have multiple ligands, especially, as in the current case, when the receptors are expressed on numerous and divergent cell types. [Action, page 7]

Applicants respectfully remind the USPTO that it is the *ordinary skilled artisan,* not the specification or the claims, that must be enabled to make and use the claimed invention. The USPTO asserts that the specification enables the ordinary skilled artisian to make and use only nucleic acids encoding the ligands represented in SEQ ID NOS:2 or 6, or the truncated versions thereof. Applicants thank the USPTO for first acknowledging such enablement. However, applicants submit that the enabling disclosure does not stop there. Enablement is based on what the ordinary skilled artisan is able to do in view of the specification and all of the information in the art. Certainly, the specification provides the ordinary artisan with sufficient information to make and use flt3-L that has a length equal to or greater than the truncated version (amino acid #163 for SEQ ID NO:2 or amino acid #160 for SEQ ID NO:6), but equal to or less than the full length version (amino acid #231 for SEQ ID NO:2 or amino acid #235

for SEQ ID NO:6). That is, since both the truncated version and the full-length protein are enabled, then polypeptides having an intermediate length must also be enabled. In addition, the specification describes a routine procedure for making variants and muteins of flt3-L, which techniques will not be reiterated here. It cannot be disputed that such techniques are routine matters for persons having ordinary skill in the art and require no inventive thought or actions by the artisan. Furthermore, it should be mentioned that in this art of biotechnology, the level of ordinary skill is very high. Therefore, knowledge of a variety of sophisticated techniques and methods is presumed. It only requires routine methodology to construct a DNA that encodes a polypeptide capable of binding to flt3 and that is at least 80% identical to a predetermined polypeptide; it also requires routine methodology to test whether such DNA constructs will hybridize under the claimed conditions to another DNA having a predetermined sequence. This is all that applicants are claiming. Simply because the applicants do not provide "assurances" as to which variants or muteins will work and which will not work does not provide a legally sufficient reason to object to the specification. It is also immaterial whether such preparation and testing is "time consuming." What is important is whether the ordinary skilled artisan will be required to use inventive thought in order to prepare and test the DNAs. If a DNA construct fails to bind flt3 or fails to hybridize under the moderately stringent conditions, then it is not covered under the claims. See *In re Angstadt*. 190 USPQ 214 (CCPA 1976). No undue experimentation is required to make and use the claimed DNA.

Moreover, simply because a receptor can be located on "numerous and divergent" cell types does not automatically mean that the receptor has "multiple ligands." This is especially true in the instant record where the USPTO has failed to provide any scientific support for such a multiple ligand theory. Nowhere in the record has the USPTO established that multiple ligands actually exist for the flt3 receptor. The USPTO utilizes qualifying verbiage such as "it is likely that there are multiple ligands", while failing to provide scientific support for such a statement. This is merely speculation on the part of the USPTO and applicants' specification cannot be objected to based on such unsupported scientific speculation.

It is indeed true that applicants have discovered an alternate spliced variant (clone #5H) of the clone #6C. It is specifically stated in the specification that the differences between #6C and #5H also occur in regions other than in the flt3-binding extracellular domain. Thus, it would be expected by the ordinary skilled artisan that such flt3-binding region is not variant and thus clone #5H also would be capable of binding to flt3. In fact, the USPTO has already stated that one of ordinary skill in the art would be enabled to make and use the *truncated* flt3-L molecules as claimed. This being true, it follows logic and scientific principle that if an alternate spliced flt3-L variant possesses the amino acid sequence of a truncated molecule, regardless of the remaining amino acid sequences in the transmembrane region or the cytoplasmic domain, such alternate spliced variant would be expected to also bind flt3. Therefore, such variant flt3-L must also be found to be sufficiently described in the specification. Additionally, the USPTO briefly states that "undue experimentation" would be

required for the ordinary skilled artisan to obtain such an alternate spliced variant. Applicants disagree, since at page 33, the specification states that clone 5H:

> is identical to the #6C clone beginning at nucleotide 49 and continuing through nucleotide 545 (corresponding to amino acid 163) of SEQ ID NO:1. The #56H clone completely differs from that point onward... [emphasis added]

One of ordinary skill in the art would use the routine procedures of generating nucleic acid probes based on the nucleotides 49-545 of SEQ ID NO:1 and probing the cDNA library with such probe(s) of the same CV-1/EBNA cells. It is indisputable that such techniques are routine and would require no inventive thought of the ordinary artisan. Therefore, such variants are supported by a description that is sufficient to enable the skilled artisan to make and use same.

The USPTO further objects to the applicants' use of the name "flt3-L" in describing their invention. The USPTO is respectfully reminded that it is well-established law that applicants' claims are part of the specification and the claims are not to be read in a vacuum. The invention must be considered as a whole, in view of the teachings of the specification. No other physical data or characteristics are required to be recited in the claims. The specification defines "flt3-L" clearly and unambiguously. Therefore, in view of the teaching in the specification, the term "flt3-L" does have a defined meaning that would permit the reader to determine whether or not they were infringing upon applicants' claimed invention.

The USPTO has also objected to the specification's use of hybridizing language, and has rejected claim 12 based on the same. In short, the USPTO believes such use of hybridizing language is too-broad, and thus is allegedly not supported by an enabling disclosure. On page 9 of the Action, the USPTO alleges that it would be "time consuming" to prepare all of the DNA sequences within the claims "with the assurance" that they will hybridize under the specific conditions. At the outset, the USPTO has cited *Ex parte Forman* 230 USPQ 546. Nowhere in that case does the court state that the factors for determining "undue experimentation" include the amount of *time consumed*, or whether there exist *assurances* in the specification that such DNA sequences will hybridize. Therefore, such considerations are of no importance in determining whether undue experimentation will be needed.

Moreover, in an apparent contradiction with the preceding paragraph, the USPTO has stated:

> The language of "DNA that hybridizes under moderately stringent conditions to ..." literally covers all future mutations or modifications of the DNA sequences, because the claimed sequences would be expected to hybridize to all future sequences, even those not contemplated by Applicants at the time the invention was made. [Action, page 9, emphasis added]

The bold language contradicts the USPTO's allegations of undue experimentation and the applicants' alleged failure to provide "assurances" of success. The USPTO believes such

DNA sequences "would be expected to hybridize" and thus, confirms applicants' statements that such claims are supported by an enabling disclosure. Further, there is nothing improper about claiming embodiments that are "not contemplated by applicants at the time the invention was made." The Patent Statute states nothing about limiting patent claims to only those embodiments actually known to the inventors at the time the application is filed.

The USPTO has also stated how, initially, inventors intended the term "hybridize" to mean "homologous DNA obtained from other species." While that may well have been the initial intent of some applicants, unless the allowed claims actually recited such language, the *intent* behind the term "hybridize" is irrelevant. When determining infringement of a patent claim, what the applicant "intended" to mean by the claim language is not a consideration. Only the language of the claim is used to determine the scope of the invention. If the claim did not state "homologous DNA obtained from other species", then the claim would not be limited to such, regardless of the patentees intent. Infringement would be determined on whether the allegedly infringing DNA would hybridize under the conditions recited. Therefore, the USPTO's argument of the intent behind applicants claim language is of no moment.

Applicants further prove that their claims reciting the "hybridizing language" are supported by an enabling disclosure. Indeed, many patents have issued from the USPTO that utilize the same language that is being objected to in the instant application. For example, 4,703,008; 4,968,607; 5,371,193; 5,116,738; 4,956,281; 5,037,756; 5,081,019; 5,141,856; 5,231,012; 4,530,901 and 5,378,819. Moreover, it is axiomatic that the ordinary skilled artisan is well versed in the state of the art. That is, the ordinary skilled artisan is presumed to know all that is in the public domain. That being the case, the ordinary skilled artisan, having knowledge of the above-listed U.S. Patents would recognize that the claim term "hybridize" is a standard term in the art. Applicants, being their own lexicographers, have not expressly altered the ordinary meaning of the term. Therefore, the ordinary meaning of the term "hybridize" must be used. That is, the meaning used in the specifications of these patents and other publications. For example, in U.S. Patent No. 5,371,193, claim 3 recites:

> 3. An isolated mature IL-11 having IL-11 activity and encoded by a DNA sequence as in SEQ ID NO:1 or 3, or a DNA sequence capable of hybridizing thereto under stringent conditions.

The ordinary skilled artisan would find such language to be standard in the art. Indeed, the disclosures of each of the patents whose claims utilize the hybridizing language presumably provide the artisan with the information needed to determine whether such DNA fell within the scope of the claims. As stated supra, applicants have not given the claimed functional hybridizing language a meaning that is different from what is routinely used in the art. Therefore, it must be presumed that the ordinary skilled artisan is fully capable of understanding and performing the invention as claimed.The artisan would recognize that only *routine* procedures are required to make the nucleic acid sequences that are within the scope of

the claims. The USPTO, on the other hand, has not shown that the making or the using of the claimed hybridizing nucleic acid sequences would require the use of inventive steps. Only the allegation that such procedure would be "time consuming" is provided by the USPTO. As stated above, the amount of time consumed performing an experiment is not relevant to whether such experimentation is "undue." This is well-established law.

Claims that utilize such hybridizing language are no different than any other claim that defines what the compound *does* rather than what the compound *is*. Such claim types utilize what is called "functional language." The use of functional language in claim drafting is a practice sanctioned by §112:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material or acts described in the specification and equivalents thereof. [emphasis added]

There is nothing intrinsically wrong in defining something by what it does rather than what it is. *In re Hallman*, 210 USPQ 609 (CCPA 1981). A claim is not indefinite merely because it is functional. *In re Miller*, 169 USPQ 597 (CCPA 1971). Functional language is permissible in chemical cases. See *In re Barr*, 170 USPQ 330 (CCPA 1971).

In the instant claim 12, applicants are claiming a chemical compound that has very specific functional requirements. First, the DNA must hybridize with a specified cDNA of part (a) or (b) under specified conditions. Second, the polypeptide encoded by the DNA must bind flt3. Third, the polypeptide encoded by the DNA must be at least 80% identical to a polypeptide encoded by the cDNA of part (a) or (b). Clearly, claim 12 sets forth the limits for what characteristics a DNA must possess to be within the scope of the claim.

In addition, the USPTO is referred to the seminal case, *In re Angstadt*, 190 USPQ 214 (CCPA 1976). In *Angstadt*, the appellant claimed an improved process for the catalytic oxidation of secondary or tertiary alkylaromatic hydrocarbons of a specified formula. The claim recited the functional language: "to *form a reaction mixture* comprising the corresponding hydroperoxides... (emphasis added)." The examiner rejected the claims and the CCPA reversed the board's affirmation of such rejection. The CCPA held:

> [t]he process discovered by appellants is not complicated, and there is no indication that special equipment or unusual reaction conditions must be provided when practicing the invention.

Here, as in *Angstadt*, the functional claim language does not require the ordinary skilled artisan to use special equipment or unusual reaction conditions. If the rejection is maintained after consideration of the above, the USPTO is requested to make of record the specific reasons why the ordinary skilled artisan would not be able to utilize routine methods to prepare a finite number of nucleic acid sequences and test them, according to the claim. If the maintenance of

the rejection is based upon facts known personally to the Examiner, then applicants respectfully request the Examiner to set forth such facts in an affidavit according to 37 CFR §1.107(b). Withdrawal of the objection/rejection is respectfully requested.

REJECTIONS OVER PRIOR ART:

Claims 8-27 stand rejected under 35 U.S.C. 103 as allegedly being obvious over U.S. Patent Number 5,185,438 (Lemischka). It is alleged in the Action at page 10, that:

> Lemischka discloses the murine flk2 receptor, and *suggests* cloning and isolation of the ligand to the claimed receptor, to be used to stimulate the proliferation and/or differentiation of primitive stem cells. [emphasis added]

Applicants respectfully disagree. The USPTO is referred to the recent decision of the United States Court of Appeals for the Federal Circuit in *In re Deuel*, 34 USPQ 2d 1210 (Fed. Cir. 1995). In *Deuel*, the appellant claimed all DNA sequences encoding human or bovine HBGFs. The examiner in *Deuel* rejected the claims under §103 arguing that a reference that taught the N-terminal amino acid sequence of human or bovine HBGFs when combined with the general cloning methods taught by Maniatis et al., rendered the appellants' claims obvious. The CAFC reversed the Board's affirmation of the rejection, and stated:

> while the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from [prior art's] teachings, and the knowledge that some gene existed may have been clear, the precise cDNA molecules of claims 5 and 7 would not have been obvious over the [prior art] because [the prior art] teaches proteins, not the claimed or closely related DNA molecules.

Similarly to the situation in *Deuel*, Lemischka does not disclose any cDNA or polypeptide molecules for applicants' claimed flt3-L. Indeed, Lemischka discloses even less than the prior art disclosed in *Deuel*. Lemischka suggests an allegedly obvious method for *trying* to isolate the flt3-L molecules; however, that does not render obvious the subject matter of applicants' claims. Lemischka simply discloses a suggestion, or a *research plan* and nothing more. Indeed, while the general idea of a desire to obtain the claimed flt3-L DNA molecules and their function may have been obvious from Lemischka's teachings, along with the knowledge that somewhere the ligand for the flk-2 receptor existed, this information would not have rendered the claimed flt3-L cDNA molecules obvious over Lemischka. Lemischka teaches an entirely different protein, i.e., one not closely related structurally to applicants' claimed flt3-L. Thus, one skilled in the art could not have conceived of the specific flt3-L cDNA as claimed based on Lemischka's disclosure because, until applicants' flt3-L was actually isolated and its cDNA cloned, it would have been highly unlikely for one skilled in the art to contemplate what was ultimately obtained. As was held in *Deuel*, "what cannot be contemplated or conceived cannot be obvious."

The USPTO's theory that one skilled in the art might be motivated to try to do what applicants have accomplished amounts to speculation and an impermissible hindsight reconstruction of applicants' claimed invention. A general motivation to search for some protein that exists does not necessarily make obvious a specifically-defined protein or gene that is subsequently obtained as a result of that search. More information is needed, and it is not found in Lemischka. The existence of a general *method* of isolating protein or DNA molecules is essentially irrelevant to the question whether the specific molecules *themselves* would have been obvious. While there may have been a general *motivation* to isolate flt3-L and clone the respective DNA, that does not necessarily make obvious the particular flt3-L protein or DNA. Indeed, "obvious to try" is not the standard under §103. A general incentive does not make obvious a particular result. *In re Deuel.* In summary, the fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious.

In point of fact, Lemischka himself tried to clone applicants' claimed flt3-L using the same methods disclosed in the cited Lemischka patent. Reference is made to WO 95/00554 wherein Lemischka report the alleged isolation and cloning of the flt3-L. However, a close analysis of the amino acid sequence disclosed in WO 95/00554 illustrates that Lemischka failed to identify flt3-L as claimed by applicants. Indeed, the amino acid sequence identified and disclosed by Lemischka to be the flt3-L, is not. There is absolutely no sequence homology between the flt3-L claimed by applicants and the molecule disclosed by Lemischka in WO 95/00554. Therefore, there is proof that Lemischka himself could not even obtain applicants' claimed flt3-L using the procedures he disclosed in U.S. 5,185,438. Thus, applicants' flt3-L could not have been obvious.

Because the flt3-L DNA was not obvious, the remaining claims to vectors, host cells, antibodies against flt3-L, and processes for producing therefore cannot be held obvious. Reversal of the obviousness rejection is requested.

The USPTO also has alleged that claims 8-27 are obvious over Flanagan (*Cell*, 63:185) and Rosnet et al., *Oncogene*, 6:1641 in view of Lemischka. The USPTO alleges that it would have been obvious to "use the method disclosed by Flanagan et al. to identify the ligand to the flt3 receptor disclosed by Rosnet et al...." (emphasis added).

Again, applicants disagree with the USPTO's allegation of obviousness of the claimed invention. The emphasized language from the above quotation of the USPTO ("use the method") is an indication that the USPTO is using impermissible hindsight reconstruction of applicants' claimed invention. Indeed, it is apparent that the USPTO has focused on the obviousness of the *method* of cloning and not on the obviousness of the actual compound claims themselves. The USPTO is also using the improper standard of "obvious to try" which is different from the obviousness of the clamed compounds themselves. Moreover, the same

principles of law outlined above in response to the first rejection over Lemischka (U.S. 5,185,438) are equally applicable to the instant rejection. A general incentive does not make obvious a particular result. Indeed, the fact that one can conceive of a general research plan in advance for preparing an undefined compound does not mean that such specific compound was precisely envisioned and therefore obvious. Notwithstanding any of the above reasons to withdraw the rejection, Section 103 states that "patentability shall not be negatived by the manner in which the invention was made." Thus, applicants' claimed flt3-L cDNA, vectors, host cells and processes for production of flt3-L were not obvious over a general method of cloning disclosed by Flanagan et al. and Rosnet et al. in view of Lemischka. Withdrawal of the rejection is respectfully requested.

In summary, applicants have shown that the claims are in condition for allowance and respectfully request the issuance of a favorable action upon reconsideration.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service in an envelope addressed to: The Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date indicated below.

October 23, 1995
Date

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